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(71) Applicant (*for all designated States except US*): **TAISHO PHARMACEUTICAL CO., LTD.** [JP/JP]; 24-1, Takada 3-chome, Toshima-ku, Tokyo, 1708633 (JP).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **NAKAZATO, Atsuro** [JP/JP]; c/o Taisho Pharmaceutical Co., Ltd., 24-1, Takada 3-chome, Toshima-ku, Tokyo, 1708633 (JP). **OKUBO, Taketoshi** [JP/JP]; c/o Taisho Pharmaceutical Co., Ltd., 24-1, Takada 3-chome, Toshima-ku, Tokyo, 1708633 (JP). **NOZAWA, Dai** [JP/JP]; c/o Taisho Pharmaceutical Co., Ltd., 24-1, Takada 3-chome, Toshima-ku, Tokyo, 1708633 (JP). **KENNIS, Ludo, E., J.** [BE/BE]; c/o Janssen Pharmaceutica N.V., Turnhoutseweg 30, Beerse, B-2340 (BE). **DE BRUYN, Marcel, F., L.** [BE/BE]; c/o Janssen Pharmaceutica N.V., Turnhoutseweg 30, Beerse, B-2340 (BE).

(74) Agents: **ASAMURA, Kiyoshi** et al.; Room 331, New Ohtemachi Bldg., 2-1, Ohtemachi 2-chome, Chiyoda-ku, Tokyo 1000004 (JP).

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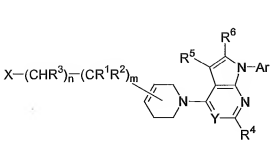
(54) Title: PYRROLOPYRIMIDINE AND PYRROLOPYRIDINE DERIVATIVES SUBSTITUTED WITH TETRAHYDROPYRIDINE AS CRF ANTAGONISTS



[I]

(57) Abstract: [PROBLEM TO BE SOLVED] An object of the present invention is to provide an antagonist against CRF receptors which is effective as a therapeutic or prophylactic agent for diseases in which CRF is considered to be involved, such as depression, anxiety, Alzheimer's disease, Parkinson's disease, Huntington's chorea, eating disorder, hypertension, gastrointestinal diseases, drug dependence, cerebral infarction, cerebral ischemia, cerebral edema, cephalic external wound, inflammation, immunity-related diseases, alopecia, irritable bowel syndrome, sleep disorders, epilepsy, dermatitides, schizophrenia, pain, etc. [SOLUTION] A pyrrolopyrimidine or pyrrolopyridine derivative substituted with tetrahydropyridine represented by the following formula [I]: has a high affinity for CRF receptors and is effective against diseases in which CRF is considered to be involved.

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DESCRIPTION

PYRROLOPYRIMIDINE AND PYRROLOPYRIDINE DERIVATIVES SUBSTITUTED WITH TETRAHYDROPYRIDINE AS CRF ANTAGONISTS

[DETAILED DESCRIPTION OF THE INVENTION]

[TECHNICAL FIELD]

The present invention relates to a therapeutic agent for diseases in which corticotropin releasing factor (CRF) is considered to be involved, such as depression, anxiety, Alzheimer's disease, Parkinson's disease, Huntington's chorea, eating disorder, hypertension, gastrointestinal diseases, drug dependence, cerebral infarction, cerebral ischemia, cerebral edema, cephalic external wound, inflammation, immunity-related diseases, alopecia, irritable bowel syndrome, sleep disorders, epilepsy, dermatitides, schizophrenia, pain, etc.

[DESCRIPTION OF THE PRIOR ART]

CRF is a hormone comprising 41 amino acids (Science, 213, 1394-1397, 1981; and J. Neurosci., 7, 88-100, 1987), and it is suggested that CRF plays a core role in biological reactions against stresses (Cell. Mol. Neurobiol., 14, 579-588, 1994; Endocrinol., 132, 723-728, 1994; and Neuroendocrinol. 61, 445-452, 1995). For CRF, there are the following two paths: a path by which CRF acts on peripheral immune system or sympathetic nervous system through hypothalamus-pituitary-adrenal system, and a path by which CRF functions as a neurotransmitter in central nervous system (in Corticotropin Releasing Factor: Basic and Clinical Studies of a Neuropeptide, pp. 29-52, 1990). Intraventricular administration of CRF to hypophysectomized rats and normal rats causes an anxiety-like symptom in both types of rats (Pharmacol. Rev., 43, 425-473, 1991; and Brain Res. Rev., 15, 71-100, 1990). That is, there are suggested the participation of CRF in hypothalamus-pituitary-adrenal system and the pathway by which CRF functions as a neurotransmitter in central nervous system.

The review by Owens and Nemeroff in 1991 summarizes diseases in which CRF is involved (Pharmacol. Rev., 43, 425-474, 1991). That is, CRF is involved in depression, anxiety, Alzheimer's disease, Parkinson's disease, Huntington's chorea, eating disorder, hypertension, gastrointestinal diseases, drug dependence, inflammation, immunity-related diseases, etc. It has recently been reported that CRF is involved also in epilepsy, cerebral infarction, cerebral ischemia, cerebral edema, and cephalic external wound (Brain Res. 545, 339-342, 1991; Ann. Neurol. 31, 48-498, 1992; Dev. Brain Res. 91, 245-251, 1996; and Brain Res. 744, 166-170, 1997). Accordingly, antagonists against CRF receptors are useful as therapeutic agents for the diseases described above.

WO04/058767, WO02/002549 and WO00/053604 disclose pyrrolopyridine and pyrrolopyrimidine derivatives as CRF receptor antagonists. However, none disclose the compounds provided in the present invention.

[PROBLEM(S) TO BE SOLVED BY INVENTION]

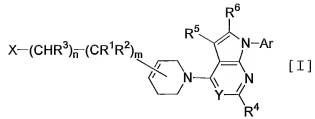
An object of the present invention is to provide an antagonist against CRF receptors which is effective as a therapeutic or prophylactic agent for diseases in which CRF is considered to be involved, such as depression, anxiety, Alzheimer's disease, Parkinson's disease, Huntington's chorea, eating disorder, hypertension, gastrointestinal diseases, drug dependence, cerebral infarction, cerebral ischemia, cerebral edema, cephalic external wound, inflammation, immunity-related diseases, alopecia, irritable bowel syndrome, sleep disorders, epilepsy, dermatitides, schizophrenia, pain, etc.

[MEANS FOR SOLVING PROBLEM]

The present inventors earnestly investigated pyrrolopyrimidine and pyrrolopyridine derivatives substituted with tetrahydropyridine that have a high affinity for CRF receptors, whereby the present invention has been accomplished.

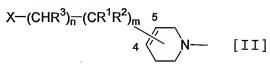
The present invention is pyrrolopyrimidine and pyrrolopyridine derivatives substituted with tetrahydropyridine explained below.

A pyrrolopyrimidine or pyrrolopyridine derivative substituted with tetrahydropyridine represented by the following formula [I]:



[I]

(wherein the tetrahydropyridine is represented by the following formula [II]:



[II]

in which the tetrahydropyridine ring is substituted with a group represented by $-(CR^1R^2)_m-(CHR^3)_n-X$ at the 4-position or 5-position of the tetrahydropyridine ring;

X is hydroxy, cyano, $-CO_2R^7$ or $-CONR^{7a}R^{7b}$;

Y is N or CR^8;

with the proviso that when Y is CR^8, then X is hydroxy;

R^1 is hydrogen, hydroxy, C_{1-5}alkyl, C_{1-5}alkoxy-C_{1-5}alkyl or hydroxy-C_{1-5}alkyl;

R^2 is hydrogen or C_{1-5}alkyl;

R^3 is hydrogen, cyano, C_{1-5}alkyl, C_{1-5}alkoxy-C_{1-5}alkyl or hydroxy-C_{1-5}alkyl;

m is an integer selected from 0, 1, 2, 3, 4 and 5;

n is 0 or 1;

with the proviso that when X is hydroxy or $-CONR^{7a}R^{7b}$, and n is 0, then m is an integer selected from 1, 2, 3, 4 and 5;

R^4 is hydrogen, halogen, C_{1-5}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkyl-C_{1-5}alkyl, hydroxy, C_{1-5}alkoxy, C_{3-8}cycloalkyloxy or $-N(R^9)R^{10}$;

R^5 and R^6 are the same or different, and independently are hydrogen, halogen, C_{1-5}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkyl-C_{1-5}alkyl, hydroxy, C_{1-5}alkoxy, C_{3-8}cycloalkyloxy, $-N(R^{11})R^{12}$, $-CO_2R^{13}$, cyano, nitro, C_{1-5}alkylthio, trifluoromethyl or trifluoromethoxy; or R^5 and R^6 are taken together to form $-CH_2-CH_2-CH_2-CH_2-$ or $-CH=CH-CH=CH-$;

with the proviso that when R^5 and R^6 are taken together to form $-CH_2-CH_2-CH_2-$

CH_2-, then X is hydroxy;

R^7 is hydrogen or C_{1-5}alkyl;

R^{7a} and R^{7b} are the same or different, and independently hydrogen or C_{1-5}alkyl;

R^8 is hydrogen, C_{1-5}alkyl, halogen, cyano or $-CO_2R^{14}$;

R^9 and R^{10} are the same or different, and independently are hydrogen, C_{1-5}alkyl, C_{3-8}cycloalkyl or C_{3-8}cycloalkyl-C_{1-5}alkyl;

R^{11} and R^{12} are the same or different, and independently are hydrogen, C_{1-5}alkyl, C_{3-8}cycloalkyl or C_{3-8}cycloalkyl-C_{1-5}alkyl;

R^{13} is hydrogen or C_{1-5}alkyl;

R^{14} is hydrogen or C_{1-5}alkyl;

Ar is aryl or heteroaryl which aryl or heteroaryl is unsubstituted or substituted with 1 or more substituents, which are the same or different, selected from the group consisting of halogen, C_{1-5}alkyl, C_{3-8}cycloalkyl, C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-5}alkoxy, C_{1-5}alkylthio, C_{1-5}alkylsulfinyl, C_{1-5}alkylsulfonyl, cyano, nitro, hydroxy, $-CO_2R^{15}$, $-C(=O)R^{16}$, $-CONR^{17}R^{18}$, $-OC(=O)R^{19}$, $-NR^{20}CO_2R^{21}$, $-S(O)_rNR^{22}R^{23}$, trifluoromethyl, trifluoromethoxy, difluoromethoxy, fluoromethoxy, methylenedioxy, ethylenedioxy and $-N(R^{24})R^{25}$;

R^{15} is hydrogen, C_{1-5}alkyl, C_{3-8}cycloalkyl or C_{3-8}cycloalkyl-C_{1-5}alkyl;

R^{16} is hydrogen or C_{1-5}alkyl;

R^{17} and R^{18} are the same or different, and independently are hydrogen, C_{1-5}alkyl, C_{3-8}cycloalkyl or C_{3-8}cycloalkyl-C_{1-5}alkyl;

R^{19} is hydrogen or C_{1-5}alkyl;

R^{20} is hydrogen or C_{1-5}alkyl;

R^{21} is hydrogen or C_{1-5}alkyl;

R^{22} and R^{23} are the same or different, and independently are hydrogen, C_{1-5}alkyl, C_{3-8}cycloalkyl or C_{3-8}cycloalkyl-C_{1-5}alkyl;

R^{24} and R^{25} are the same or different, and independently are hydrogen, C_{1-5}alkyl, C_{3-8}cycloalkyl or C_{3-8}cycloalkyl-C_{1-5}alkyl;

r is 1 or 2), individual isomers thereof, racemic or non-racemic mixtures of isomers thereof or N-oxide thereof, or pharmaceutically acceptable salts and hydrates thereof.

The terms used in the present specification have the following meanings.

The term "C_{1-5}alkyl" means a straight chain or branched chain alkyl group of 1 to 5 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *t*-butyl, *sec*-butyl, pentyl, isopentyl or the like.

The term "C_{1-5}alkoxy" means a straight chain or branched chain alkoxy group of 1 to 5 carbon atoms, such as methoxy, ethoxy, propoxy, isopropyloxy, butoxy, isobutyloxy, pentyloxy, isopentyloxy or the like.

The term "C_{1-5}alkoxy-C_{1-5}alkyl" means a substituted C_{1-5}alkyl group having the above-mentioned C_{1-5}alkoxy group as the substituent, such as methoxymethyl, 2-methoxyethyl, 2-ethoxyethyl or the like.

The term "hydroxy-C_{1-5}alkyl" means a substituted C_{1-5}alkyl group having hydroxy group, such as hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1-hydroxypropyl, 2-hydroxypropyl, 3-hydroxypropyl, 4-hydroxybutyl, 5-hydroxypentyl or the like.

The term "C_{3-8}cycloalkyl" means a cyclic alkyl group of 3 to 8 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or the like.

The term "C_{3-8}cycloalkyl-C_{1-5}alkyl" means a substituted C_{1-5}alkyl group having the above-mentioned C_{3-8}cycloalkyl as the substituent, such as cyclopropylmethyl, cyclopropylethyl, cyclopentylethyl or the like.

The term "C_{3-8}cycloalkyloxy" means a cyclic alkoxy group of 3 to 8 carbon atoms, such as cyclopropyloxy, cyclobutyloxy, cyclopentyloxy or the like.

The term "C_{1-5}alkylthio" means a straight chain or branched chain alkylthio group of 1 to 5 carbon atoms, such as methylthio, ethylthio, propylthio, isopropylthio or the like.

The term "halogen" means fluorine, chlorine, bromine or iodine atom.

The term "aryl" means a monocyclic or bicyclic group of 6 to 12 ring carbon atoms having at least one aromatic ring, such as phenyl, naphthyl or the like.

The term "heteroaryl" means a monocyclic or bicyclic group of 5 to 12 ring atoms having at least one aromatic ring having in its ring 1 to 4 atoms which may be the same or different and are selected from nitrogen, oxygen and sulfur, such as pyridyl, pyrimidinyl, imidazolyl, quinolyl, indolyl, benzofuranyl, quinoxalinyl, benzo[1,2,5]thiadiazolyl, benzo[1,2,5]oxadiazolyl or the like.

The term "C_{2-5}alkenyl" means a straight chain or branched chain alkenyl

group of 2 to 5 carbon atoms, such as vinyl, isopropenyl, allyl or the like.

The term "C_{2-5}alkynyl" means a straight chain or branched chain alkynyl group of 2 to 5 carbon atoms, such as ethynyl, prop-1-ynyl, prop-2-ynyl or the like.

The term "C_{1-5}alkysulfinyl" means a straight chain or branched chain alkylsulfinyl group of 1 to 5 carbon atoms, such as methanesulfinyl, ethanesulfinyl or the like.

The term "C_{1-5}alkysulfonyl" means a straight chain or branched chain alkylsulfonyl group of 1 to 5 carbon atoms, such as methanesulfonyl, ethanesulfonyl or the like.

The term "aryl or heteroaryl which aryl or heteroaryl is unsubstituted or substituted with 1 or more substituents, which are the same or different, selected from the group consisting of halogen, C_{1-5}alkyl, C_{3-8}cycloalkyl, C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-5}alkoxy, C_{1-5}alkylthio, C_{1-5}alkylsulfinyl, C_{1-5}alkylsulfonyl, cyano, nitro, hydroxy, $-CO_2R^{15}$, $-C(=O)R^{16}$, $-CONR^{17}R^{18}$, $-OC(=O)R^{19}$, $-NR^{20}CO_2R^{21}$, $-S(O)_nNR^{22}R^{23}$, trifluoromethyl, trifluoromethoxy, difluoromethoxy, fluoromethoxy, methylenedioxy, ethylenedioxy and $-N(R^{24})R^{25}$" includes, for example, 2,4-dimethylphenyl, 2,6-dimethylphenyl, 2,4-dibromophenyl, 2-bromo-4-isoproylphenyl, 2,4-dichlorophenyl, 2,6-dichlorophenyl, 2-chloro-4-trifluoromethylphenyl, 4-methoxy-2-methylphenyl, 2-chloro-4-trifluoromethoxyphenyl, 4-isopropyl-2-methylthiophenyl, 2,4,6-trimethylphenyl, 4-bromo-2,6-dimethylphenyl, 4-bromo-2,6-diethylphenyl, 4-chloro-2,6-dimethylphenyl, 2,4,6-tribromophenyl, 2,4,5-tribromophenyl, 2,4,6-trichlorophenyl, 2,4,5-trichlorophenyl, 4-bromo–2,6-dichlorophenyl, 6-chloro-2,4-dibromophenyl, 2,4-dibromo-6-fluorophenyl, 2,4-dibromo-6-methylphenyl, 2,4-dibromo-6-methoxyphenyl, 2,4-dibromo-6-methylthiophenyl, 2,6-dibromo-4-isopropylphenyl, 2,6-dibromo-4-trifluoromethylphenyl, 2-bromo-4-trifluoromethylphenyl, 4-bromo-2-chlorophenyl, 2-bromo-4-chlorophenyl, 4-bromo-2-methylphenyl, 4-chloro-2-methylphenyl, 2,4-dimethoxyphenyl, 2,6-dimethyl-4-methoxyphenyl, 4-chloro-2,6-dibromophenyl, 4-bromo-2,6-difluorophenyl, 2,6-dichloro-4-trifluoromethylphenyl, 2,6-dichloro-4-trifluoromethoxyphenyl, 2,6-dibromo-4-trifluoromethoxyphenyl, 2-chloro-4,6-dimethylphenyl, 2-bromo-4,6-dimethoxyphenyl, 2-bromo-4-isopropyl-6-methoxyphenyl, 2,4-dimethoxy-6-methylphenyl, 6-dimethylamino-4-methylpyridin-3-yl, 2-chloro-6-trifluoromethylpyridin-3-yl, 2-chloro-6-

trifluoromethoxypyridin-3-yl, 2-chloro-6-methoxypyridin-3-yl, 6-methoxy-2-trifluoromethylpyridin-3-yl, 2-chloro-6-difluoromethylpyridin-3-yl, 6-methoxy-2-methylpyridin-3-yl, 2,6-dimethoxypyridin-3-yl, 4,6-dimethyl-2-trifluoromethylpyrimidin-5-yl, 2-dimethylamino-6-methylpyridin-3-yl, 6-dimethylamino-2-methylpyridin-3-yl, 2,3-dihydrobenzo[1,4]dioxin-5-yl and benzo[1,3]dioxol-4-yl, 5,7-dimethylbenzo[1,2,5]thiadiazol-4-yl, 5,7-dimethylbenzo[1,2,5]oxadiazol-4-yl, 2-isopropoxy-6-trifluoromethylpyridin-3-yl, 2-methoxy-6-methylpyridin-3-yl, 2,6-dimethylpyridin-3-yl, 2-bromo-6-methoxypyridin-3-yl, 2-chloro-6-dimethylaminopyridin-3-yl, 2,6-dichloropyridin-3-yl, 2,4-dimethyl-6-dimethylaminopyridin-3-yl, 2,4,6-trimethylpyridin-3-yl, 2,4,6-trimethylpyrimidin-5-yl, 4,6-dimethyl-2-dimethylaminopyrimidin-5-yl, 5-iodo-3-methylpyridin-2-yl, 3-methyl-5-methylaminopyridin-2-yl, 3-dimethylamino-5-methylpyridin-2-yl, 5-methyl-3-methylaminopyridin-2-yl, 3-chloro-5-methylpyridin-2-yl, 3-amino-5-methylpyridin-2-yl, 5-methyl-3-nitropyridin-2-yl, 5-diethylamino-3-methylpyridin-2-yl, 5-fluoro-3-methylpyridin-2-yl, 5-chloro-3-methylpyridin-2-yl, 5-dimethylamino-3-methylpyridin-2-yl, 5-amino-3-methylpyridin-2-yl, 3-methyl-5-nitropyridin-2-yl, 3-bromo-5-methylpyridin-2-yl, 4-chloro-2,5-dimethoxyphenyl, 4,5-dimethyl-2-methoxyphenyl, 5-fluoro-2,4-dimethylphenyl, 2,4-dimethoxy-5-methylphenyl, 2-chloro-4-methoxy-5-methylphenyl, 2-chloro-5-fluoro-4-methylphenyl, 2-bromo-4,5-dimethoxyphenyl, 2-bromo-5-fluoro-4-methoxyphenyl, 2-chloro-4,5-dimethoxyphenyl, 2.5-dichloro-4-methoxyphenyl, 2,4-dichloro-5-fluorophenyl, 2-chloro-5-fluoro-4-methoxyphenyl, 2,4,5-trichlorophenyl, 2-chloro-5-fluoro-4-methylphenyl, 5-fluoro-4-methoxy-2-methylphenyl, 4,5-dimethoxy-2-methylphenyl, 5-chloro-4-methoxy-2-methylphenyl, 2,4,5-trimethylphenyl, 6-methoxy-4-methylpyridin-3-yl, 4-methoxy-6-methylpyridin-3-yl, 4,6-dimethylpyridin-3-yl, 2-chloro-4-isopropylphenyl, 2-chloro-4-methylphenyl, 4-amino-2-chlorophenyl, 2-chloro-4-dimethylcarbamoylphenyl, 2-chloro-4-methylcarbamoylphenyl, 4-carbamoyl-2-chlorophenyl, 2-chloro-4-methylsulfonylphenyl, 4-carboxy-2-chlorophenyl, 2-chloro-4-iodophenyl, 2-bromo-4-methylthiophenyl, 2-bromo-4-methylsulfinylphenyl, 2-bromo-4-dimethylaminophenyl, 2-bromo-4-methylsulfonylphenyl, 2-bromo-4-cyclopentylphenyl, 2-bromo-4-*tert*-butylphenyl, 2-bromo-4-propylphenyl, 2-bromo-4-methylphenyl, 2-bromo-4-

trifluoromethoxyphenyl, 2-bromo-4-methoxyphenyl, 2-bromo-4-ethoxyphenyl, 4-isopropyl-2-methylsulfonylphenyl, 4-cyclopentyl-2-methylthiophenyl, 4-butyl-2-methylthiophenyl, 4-methoxy-2-methylthiophenyl, 2-methylthio-4-propylphenyl, 2-dimethylamino-4-isopropylphenyl, 2-iodo-4-isopropylphenyl, 2-fluoro-4-methylphenyl, 2,4-difluorophenyl, 2-chloro-4-methoxyphenyl, 2-chloro-4-hydroxyphenyl, 4-cyano-2-methoxyphenyl, 4-bromo-2-methoxyphenyl, 2-methoxy-4-methylphenyl, 4-chloro-2-methoxyphenyl, 2-hydroxy-4-methylphenyl, 4-fluoro-2-methoxyphenyl, 2-hydroxy-4-methylphenyl, 4-cyano-2-methoxyphenyl, 2-chloro-4-methylthiophenyl, 2-methoxy-4-trifluoromethylphenyl, 4-isopropyl-2-methoxyphenyl, 2-chloro-4-cyanophenyl, 2-chloro-4-ethoxycarbonylphenyl, 2-chloro-4-methylaminophenyl, 4-cyano-2-trifluoromethylphenyl, 4-cyano-2-methylphenyl, 2-methyl-4-trifluoromethoxyphenyl, 2-cyano-4-trifluoromethylphenyl, 4-carboxyamino-2-trifluoromethylphenyl, 4-methoxy-2-trifluoromethylphenyl, 4-fluoro-2-methylphenyl, 4-hydroxy-2-methylphenyl, 4-methoxy-2-methoxycarbonylphenyl, 2-ethyl-4-methoxyphenyl, 2-formyl-4-methoxyphenyl, 4-chloro-2-trifluoromethylphenyl, 4-dimethylamino-2-trifluoromethylphenyl, 4-difluoromethoxy-2-methylphenyl, 2-cyano-4-methoxyphenyl, 4-hydroxy-2-trifluoromethylphenyl, 4-isopropyl-2-trifluoromethylphenyl, 4-diethylamino-2-methylphenyl, 4-fluoro-2-trifluoromethylphenyl, 4-propoxy-2-trifluoromethylphenyl, 4-dimethylamino-2-methylthiophenyl, 4-isopropyl-2-isopropylthiophenyl, 2-ethylthio-4-isopropylphenyl, 4-methylamino-2-methylthiophenyl, 2-methylthio-4-propionylphenyl, 4-acetyl-2-methylthiophenyl, 4-cyano-2-methylthiophenyl, 4-methoxy-2-methylthiophenyl, 4-ethyl-2-methylthiophenyl, 4-bromo-2-methylthiophenyl, 4-isopropyl-2-methylsulfinylphenyl, 2,4-dimethylthiophenyl, 4,6-dimethyl-2-isopropylphenyl, 4,6-dimethyl-2-isopropenylphenyl, 2-acetyl-4,6-dimethylphenyl, 2,6-dimethyl-4-trifluoromethylphenyl, 2,6-dimethyl-4-isopropenylphenyl, 4-acetyl-2,6-dimethylphenyl, 2,4,6-triethylphenyl, 4,6-dimethyl-2-methylthiophenyl, 4,6-dimethyl-2-iodophenyl, 2-fluoromethoxy-4,6-dimethylphenyl, 4,6-dimethyl-2-isopropoxyphenyl, 4,6-dimethyl-2-ethoxyphenyl, 2,6-dichloro-4-ethoxyphenyl, 2-bromo-4,6-dimethoxyphenyl, 2-bromo-6-hydroxy-4-methoxyphenyl, 2,6-dibromo-4-ethoxyphenyl, 4-bromo-2-methoxy-6-methylphenyl, 2,6-dibromo-4-methoxyphenyl, 4,6-dibromo-2-

trifluoromethoxyphenyl, 2,4-dibromo-6-trifluoromethylphenyl, 4-bromo-2-chloro-6-methylphenyl, 4-chloro-2,6-dimethoxyphenyl, 2,4-dichloro-6-methoxyphenyl, 4,6-dichloro-2-methylthiophenyl, 4,6-dichloro-2-trifluoromethylphenyl, 2,6-dimethoxy-4-ethylphenyl, 4,6-dimethyl-2-methoxyphenyl, 2,6-dimethoxy-4-methylphenyl, 2-chloro-6-methoxy-4-methylphenyl, 4,6-dimethyl-2-ethoxyphenyl, 6-hydroxy-2,4-dimethylphenyl, 4-cyano-2-methoxy-6-methylphenyl, 6-fluoro-2-methoxy-4-methylphenyl, 4-acetyl-2-methoxy-6-methylphenyl, 2-chloro-4,6-dimethoxyphenyl, 2,6-dimethoxy-4-ethoxyphenyl, 2,4,6-trimethoxyphenyl, 4,6-dibromo-2-trifluoromethoxyphenyl, 2-bromo-4-dimethylamino-6-methoxyphenyl, 4-bromo-2-methoxy-6-methylphenyl, 4,6-dimethoxy-2-propoxyphenyl, 4,6-dichloro-2-propoxyphenyl, 2-bromo-6-hydroxy-4-methoxyphenyl, 2,4,6-trifluorophenyl, 2-bromo-6-fluoro-4-methylphenyl, 4-difluoromethoxy-2,6-dimethylphenyl, 2,6-dimethyl-4-ethoxyphenyl, 2,6-dimethyl-4-isopropoxyphenyl, 2,6-dimethyl-4-methylthiophenyl, 2,6-dimethyl-4-methylsulfonylophenyl, 2,6-dimethyl-4-methylsulfinylophenyl, 2,3-dichlorophenyl, 4-methoxy-2,3-dimethylphenyl, 2-chloro-3-fluoro-4-methoxyphenyl, 2,3,4-trichlorophenyl, 4-methoxy-2,5-dimethylphenyl.

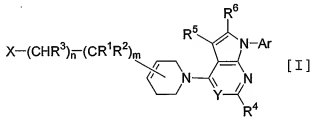
The "pharmaceutically acceptable salts" in the present invention include, for example, salts with an inorganic acid such as sulfuric acid, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid or the like; salts with an organic acid such as acetic acid, oxalic acid, lactic acid, tartaric acid, fumaric acid, maleic acid, citric acid, benzenesulfonic acid, methanesulfonic acid, *p*-toluenesulfonic acid, benzoic acid, camphorsulfonic acid, ethanesulfonic acid, glucoheptonic acid, gluconic acid, glutamic acid, glycolic acid, malic acid, malonic acid, mandelic acid, galactaric acid, naphthalene-2-sulfonic acid or the like; salts with one or more metal ions such as lithium ion, sodium ion, potassium ion, calcium ion, magnesium ion, zinc ion, aluminium ion or the like; salts with amines such as ammonia, arginine, lysine, piperazine, choline, diethylamine, 4-phenylcyclohexylamine, 2-aminoethanol, benzathine or the like.

A compound of the present invention includes any isomers such as diastereomers, enantiomers, geometric isomers and tautomeric forms. In a compound represented by formula [I], if the cyclic amino group has one or more chiral carbons and/or if there is an axial chirality between Ar and pyrrolopyrimidine (or

pyrrolopyridine) ring, several stereoisomers (diastereomers or enantiomers) can exist. The compound of the present invention includes all of the individual isomers and the racemic and non-racemic mixtures of the isomers.

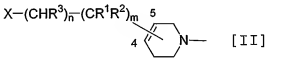
Preferable examples of the compound of the present invention are as follows.

That is, preferable are compounds represented by the following formula [I]:



[I]

(wherein the tetrahydropyridine is represented by the following formula [II]:



[II]

in which the tetrahydropyridine ring is substituted with a group represented by $-(CR^1R^2)_m-(CHR^3)_n-X$ at the 4-position or 5-position of the tetrahydropyridine ring;

X is hydroxy, cyano or $-CO_2R^7$;

Y is N or CR^8;

with the proviso that when Y is CR^8, then X is hydroxy;

R^1 is hydrogen, hydroxy, C_{1-5}alkyl, C_{1-5}alkoxy-C_{1-5}alkyl or hydroxy-C_{1-5}alkyl;

R^2 is hydrogen or C_{1-5}alkyl;

R^3 is hydrogen, cyano, C_{1-5}alkyl, C_{1-5}alkoxy-C_{1-5}alkyl or hydroxy-C_{1-5}alkyl;

m is an integer selected from 0, 1, 2, 3, 4 and 5;

n is 0 or 1;

with the proviso that when X is hydroxy, and n is 0, then m is an integer selected from 1, 2, 3, 4 and 5;

R^4 is hydrogen, C_{1-5}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkyl-C_{1-5}alkyl, hydroxy, C_{1-5}alkoxy, C_{3-8}cycloalkyloxy or $-N(R^9)R^{10}$;

R^5 and R^6 are the same or different, and independently are hydrogen, halogen, C_{1-5}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkyl-C_{1-5}alkyl, hydroxy, C_{1-5}alkoxy, C_{3-8}cycloalkyloxy, $-N(R^{11})R^{12}$, $-CO_2R^{13}$, cyano, nitro, C_{1-5}alkylthio, trifluoromethyl or trifluoromethoxy; or R^5 and R^6 are taken together to form $-CH_2-CH_2-CH_2-CH_2-$ or -CH=CH-CH=CH-;

with the proviso that when R^5 and R^6 are taken together to form $-CH_2-CH_2-CH_2-CH_2-$, then X is hydroxy;

R^7 is hydrogen or C_{1-5}alkyl;

R^8 is hydrogen, C_{1-5}alkyl, halogen, cyano or $-CO_2R^{14}$;

R^9 and R^{10} are the same or different, and independently are hydrogen, C_{1-5}alkyl, C_{3-8}cycloalkyl or C_{3-8}cycloalkyl-C_{1-5}alkyl;

R^{11} and R^{12} are the same or different, and independently are hydrogen, C_{1-5}alkyl, C_{3-8}cycloalkyl or C_{3-8}cycloalkyl-C_{1-5}alkyl;

R^{13} is hydrogen or C_{1-5}alkyl;

R^{14} is hydrogen or C_{1-5}alkyl;

Ar is aryl or heteroaryl which aryl or heteroaryl is unsubstituted or substituted with 1 or more substituents, which are the same or different, selected from the group consisting of halogen, C_{1-5}alkyl, C_{3-8}cycloalkyl, C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-5}alkoxy, C_{1-5}alkylthio, C_{1-5}alkylsulfinyl, C_{1-5}alkylsulfonyl, cyano, nitro, hydroxy, $-CO_2R^{15}$, $-C(=O)R^{16}$, $-CONR^{17}R^{18}$, $-OC(=O)R^{19}$, $-NR^{20}CO_2R^{21}$, $-S(O)_2NR^{22}R^{23}$, trifluoromethyl, trifluoromethoxy, difluoromethoxy, fluoromethoxy, methylenedioxy, ethylenedioxy and $-N(R^{24})R^{25}$;

R^{15} is hydrogen, C_{1-5}alkyl, C_{3-8}cycloalkyl or C_{3-8}cycloalkyl-C_{1-5}alkyl;

R^{16} is hydrogen or C_{1-5}alkyl;

R^{17} and R^{18} are the same or different, and independently are hydrogen, C_{1-5}alkyl, C_{3-8}cycloalkyl or C_{3-8}cycloalkyl-C_{1-5}alkyl;

R^{19} is hydrogen or C_{1-5}alkyl;

R^{20} is hydrogen or C_{1-5}alkyl;

R^{21} is hydrogen or C_{1-5}alkyl;

R^{22} and R^{23} are the same or different, and independently are hydrogen, C_{1-5}alkyl, C_{3-8}cycloalkyl or C_{3-8}cycloalkyl-C_{1-5}alkyl;

R^{24} and R^{25} are the same or different, and independently are hydrogen, C_{1-5}alkyl, C_{3-8}cycloalkyl or C_{3-8}cycloalkyl-C_{1-5}alkyl;

r is 1 or 2), individual isomers thereof, racemic or non-racemic mixtures of isomers thereof or N-oxide thereof, or pharmaceutically acceptable salts and hydrates thereof.

More preferable are compounds represented by the formula [I] in which Y is N. More preferable are compounds represented by the formula [I] in which Y is N; X is hydroxy; m is an integer selected from 1, 2, 3, 4 and 5; n is 0; R^1 and R^2 are hydrogen. More preferable are compounds represented by the formula [I] in which Y is N; X is hydroxy; m is an integer selected from 1, 2 and 3; n is 0; R^1 and R^2 are hydrogen; R^4 is C_{1-5}alkyl; R^5 and R^6 are the same or different, and independently are hydrogen or C_{1-5}alkyl; Ar is phenyl which phenyl is substituted with two or three substituents, which are the same or different, selected from the group consisting of halogen, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkylthio, trifluoromethyl, trifluoromethoxy and -N(R^{24})R^{25} (wherein R^{24} and R^{25} are the same or different, and independently are hydrogen or C_{1-3}alkyl).

Other preferable are compounds represented by the formula [I] in which Y is N; X is cyano. More preferable are compounds represented by the formula [I] in which Y is N; X is cyano; m is 0 or 1; n is 0; R^1 and R^2 are hydrogen; R^4 is C_{1-5}alkyl; R^5 and R^6 are the same or different, and independently are hydrogen or C_{1-5}alkyl; Ar is phenyl which phenyl is substituted with two or three substituents, which are the same or different, selected from the group consisting of halogen, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkylthio, trifluoromethyl, trifluoromethoxy and -N(R^{24})R^{25} (wherein R^{24} and R^{25} are the same or different, and independently are hydrogen or C_{1-3}alkyl).

Other preferable are compounds represented by the formula [I] in which Y is CR^8; X is hydroxy. More preferable are compounds represented by the formula [I] in which Y is CH; X is hydroxy; m is an integer selected from 1, 2, 3, 4 and 5; n is 0; R^1 and R^2 are hydrogen. More preferable are compounds represented by the formula [I] in which Y is CH; X is hydroxy; m is an integer selected from 1, 2 and 3; n is 0; R^1 and R^2 are hydrogen; R^4 is C_{1-5}alkyl; R^5 and R^6 are the same or different, and independently are hydrogen or C_{1-5}alkyl; Ar is phenyl which phenyl is substituted with two or three substituents, which are the same or different,

selected from the group consisting of halogen, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkylthio, trifluoromethyl, trifluoromethoxy and $-N(R^{24})R^{25}$ (wherein R^{24} and R^{25} are the same or different, and independently are hydrogen or C_{1-3}alkyl.

The preferable R^1 is hydrogen.

The preferable R^2 is hydrogen.

The preferable R^3 is hydrogen.

The preferable R^4 is C_{1-3} alkyl. The more preferable R^4 is methyl.

The preferable R^5 is C_{1-3} alkyl. The more preferable R^5 is methyl.

The preferable R^6 is hydrogen or C_{1-3} alkyl. The more preferable R^6 is hydrogen or methyl.

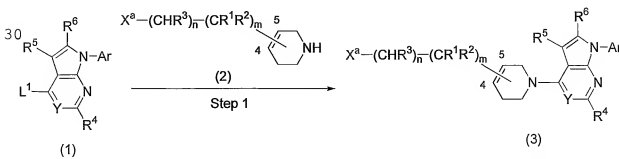
When X is hydroxy, preferable m is an integer selected from 1, 2 and 3 and preferable n is 0.

When X is cyano, preferable m is 0 or 1 and preferable n is 0.

The preferable Ar is phenyl which phenyl is substituted with two or three substituents, which are the same or different, selected from the group consisting of chloro, bromo, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkylthio, trifluoromethyl, trifluoromethoxy and dimethylamino. The more preferable Ar is is phenyl which phenyl is substituted with two or three substituents, which are the same or different, selected from the group consisting of chloro, bromo, C_{1-3}alkyl.

The compound represented by the formula [I] can be produced, for example, by the process shown in the following reaction schemes 1 and 2 [in the following reaction schemes, R^1, R^2, R^3, R^4, R^5, R^6, m, n, X, Y and Ar are as defined above; L^1 is chloro, bromo, iodo, methanesulfonyloxy, benzenesulfonyloxy, *p*-toluenesulfonyloxy or trifluoromethanesulfonyloxy group; X^a is hydroxy, cyano, $-C(=O)O-C_{1-5}$alkyl or $-CONR^{7a}R^{7b}$; R^a is C_{1-5}alkyl; R^b is C_{1-5}alkyl or phenyl; R^c is C_{1-5}alkoxy or $-NR^{7a}R^{7b}$.].

Reaction Scheme 1

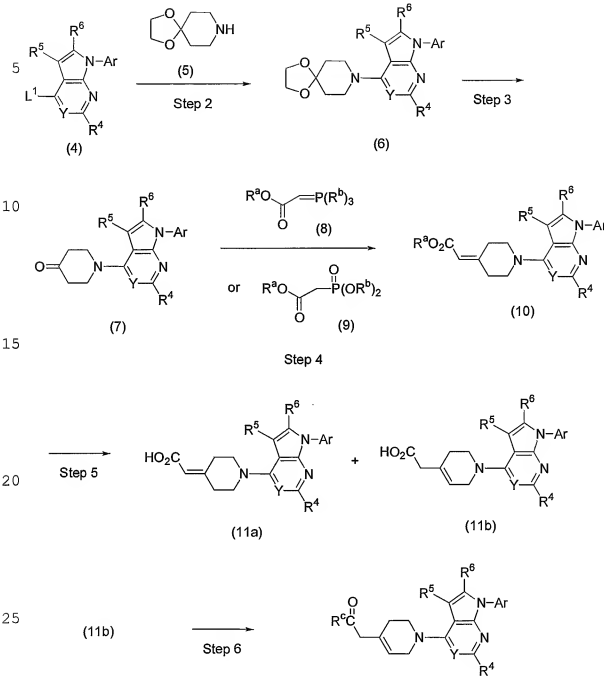


(1) (3)

Step 1:

Compound (3), a compound of the present invention, can be obtained by reacting Compound (1) with Compound (2) in an inert solvent or no solvent in the presence or absence of a base. Herein, the base includes, for example, amines such as triethylamine, *N*,*N*-diisopropylethylamine, pyridine and the like; inorganic bases such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, sodium hydroxide, potassium hydroxide, barium hydroxide, sodium hydride and the like; metal alcoholates such as sodium methoxide, sodium ethoxide, potassium *tert*-butoxide and the like; metal amides such as sodium amide, lithium diisopropylamide and the like; and Grignard reagents such as methylmagnesium bromide and the like. The inert solvent includes, for example, alcohols such as methanol, ethanol, isopropyl alcohol, ethylene glycol and the like; ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene, xylene and the like; esters such as ethyl acetate, ethyl formate and the like; amides such as *N*,*N*-dimethylformamide, *N*-methylpyrrolidone, *N*,*N*-dimethylacetamide and the like; acetonitrile; dimethyl sulfoxide; pyridine; chloroform; dichloromethane; water; and mixtures of solvents selected from these inert solvents.

Reaction Scheme 2



Step 2:

Compound (6) can be obtained by reacting Compound (4) with Compound (5) in an inert solvent or without any solvent in the presence or absence of a base. Herein, the base includes, for example, amines such as triethylamine, *N*,*N*-diisopropylethylamine, pyridine and the like; inorganic bases such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium

hydrogencarbonate, sodium hydroxide, potassium hydroxide, barium hydroxide, sodium hydride and the like; metal alcoholates such as sodium methoxide, sodium ethoxide, potassium *tert*-butoxide and the like; metal amides such as sodium amide, lithium diisopropylamide and the like; and Grignard reagents such as methylmagnesium bromide and the like. The inert solvent includes, for example, alcohols such as methanol, ethanol, isopropyl alcohol, ethylene glycol and the like; ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene, xylene and the like; esters such as ethyl acetate, ethyl formate and the like; amides such as *N,N*-dimethylformamide, *N*-methylpyrrolidone, *N,N*-dimethylacetamide and the like; acetonitrile; dimethyl sulfoxide; pyridine; chloroform; dichloromethane; water; and mixtures of solvents selected from these inert solvents.

Step 3:

Compound (6) can be converted to Compound (7) by converting the acetal to the ketone by using a method as described in *Protective Group in Organic Synthesis* (T. W. Greene, P. G. M. Wuts; 3rd ed., 1999, John Wiley & sons, Inc.).

Step 4:

Compound (7) can be converted to Compound (10) by reacting Compound (7) with Compound (8) or Compound (9) in an inert solvent in the presence or absence of a base. Herein, the base includes, for example, amines such as triethylamine, *N,N*-diisopropylethylamine, pyridine and the like; inorganic bases such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, sodium hydroxide, potassium hydroxide, barium hydroxide, sodium hydride and the like; metal alcoholates such as sodium methoxide, sodium ethoxide, potassium *tert*-butoxide and the like; metal amides such as sodium amide, lithium diisopropylamide and the like; and Grignard reagents such as methylmagnesium bromide and the like. The inert solvent includes, for example, alcohols such as methanol, ethanol, isopropyl alcohol, ethylene glycol and the like; ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene, xylene and the like; esters such as ethyl acetate, ethyl formate and the like; amides

such as *N,N*-dimethylformamide, *N*-methylpyrrolidone, *N,N*-dimethylacetamide and the like; acetonitrile; dimethyl sulfoxide; pyridine; chloroform; dichloromethane; water; and mixtures of solvents selected from these inert solvents.

Step 5:

A mixture of Compound (11a) and Compound (11b) can be obtained by conventional hydrolysis method of the ester from Compound (10) with an acid or a base in an inert solvent. Herein, the acid includes, for example, inorganic acids such as sulfuric acid, hydrochloric acid, hydrobromic acid, nitric acid or the like; organic acids such as formic acid, acetic acid, trifluoroacetic acid, benzenesulfonic acid, methanesulfonic acid, *p*-toluenesulfonic acid, trifluoromethanesulfonic acid and the like. The base includes, for example, inorganic bases such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, sodium hydroxide, potassium hydroxide, barium hydroxide and the like; The inert solvent includes, for example, alcohols such as methanol, ethanol, isopropyl alcohol, ethylene glycol and the like; ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene, xylene and the like; esters such as ethyl acetate, ethyl formate and the like; amides such as *N,N*-dimethylformamide, *N*-methylpyrrolidone, *N,N*-dimethylacetamide and the like; acetonitrile; dimethyl sulfoxide; pyridine; chloroform; dichloromethane; water; and mixtures of solvents selected from these inert solvents.

Step 6:

Compound (12), a compound of the present invention, can be synthesized from Compound (11b) by conventional methods for amidating a carboxy group, esterification of a carboxy group or alkylation of a carboxy group in the presence or absence of a base in an inert solvent. Conventional methods for amidating a carboxy group or esterification of a carboxy group are: for example, the reaction *via* a mixed acid anhydride obtained by the reaction of Compound (11b) with haloformic acid ester (e.g., ethyl chloroformate or isobutyl chloroformate) or an acid chloride (e.g., benzoyl chloride or pivaloyl chloride); the reaction in the presence of a condensing agent such as N,N'-dicyclohexylcarbodiimide (DCC), 1-

(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCl), carbonyldiimidazole (CDI), diphenylphosphorylazide (DPPA), diethyl cyanophosphate or the like, and optionally an additive such as 1-hydroxybenzotriazole (HOBt), N-hydroxysuccinimide, 4-dimethylaminopyridine or the like; or the reaction *via* an acid halide obtained by the reaction of Compound (11b) with a halogenating reagent such as thionyl chloride, oxalyl chloride, or the like; conventional methods for alkylation of a carboxy group is the reaction with an alkylating reagent such as alkylhalide or alkylsulfonate in the presence or absence of an additive to accelerate the reaction such as NaI and KI. The base includes amines such as triethylamine, N,N-diisopropylethylamine, pyridine, 1,8-diazabicyclo[5.4.0]undec-7-ene and the like; inorganic bases such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, sodium hydroxide, potassium hydroxide, lithium hydroxide, barium hydroxide, sodium hydride and the like. The inert solvent includes, for example, alcohols such as methanol, ethanol, isopropyl alcohol, ethylene glycol and the like; ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene and the like; amides such as N,N-dimethylformamide, N-methylpyrrolidone, N,N-dimethylacetamide and the like; acetonitrile; dimethyl sulfoxide; pyridine; chloroform; dichloromethane; water; and mixtures of solvents selected from these inert solvents.

The compound of the present invention can be converted to a salt in an inert solvent with an inorganic acid such as sulfuric acid, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid or the like, with an organic acid such as acetic acid, oxalic acid, lactic acid, tartaric acid, fumaric acid, maleic acid, citric acid, benzenesulfonic acid, methanesulfonic acid, *p*-toluenesulfonic acid, benzoic acid, camphorsulfonic acid, ethanesulfonic acid, glucoheptonic acid, gluconic acid, glutamic acid, glycolic acid, malic acid, malonic acid, mandelic acid, galactaric acid, naphthalene-2-sulfonic acid or the like, with an inorganic base such as lithium hydroxide, sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, zinc hydroxide, aluminum hydroxide or the like or with an organic base such as ammonia, arginine, lysine, piperazine, choline, diethylamine,

4-phenylcyclohexylamine, 2-aminoethanol, benzathine or the like. The inert solvent includes, for example, alcohols such as methanol, ethanol, isopropyl alcohol, ethylene glycol and the like; ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene and the like; esters such as ethyl acetate, ethyl formate and the like; ketones such as acetone, methylethylketone and the like; amides such as *N*,*N*-dimethylformamide, *N*-methylpyrrolidone, *N*,*N*-dimethylacetamide and the like; acetonitrile; dichloromethane; chloroform; dimethyl sulfoxide; pyridine; water; and mixtures of solvents selected from these inert solvents.

The compound of the present invention is useful as a therapeutic or prophylactic agent for diseases in which CRF is considered to be involved. For this purpose, the compound of the present invention can be formulated into tablets, pills, capsules, granules, powders, solutions, emulsions, suspensions, injections and the like by a conventional preparation technique by adding conventional fillers, binders, disintegrators, pH-adjusting agents, solvents, etc.

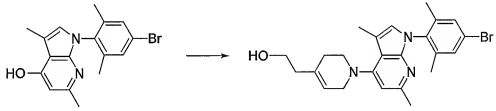
The compound of the present invention can be administered to an adult patient in a dose of 0.1 to 500 mg per day in one portion or several portions orally or parenterally. The dose can be properly increased or decreased depending on the kind of a disease and the age, body weight and symptom of a patient.

[ENBODIMENTS OF THE INVENTION]

The present invention is concretely explained with reference to the following examples and test example, but is not limited thereto.

Example 1

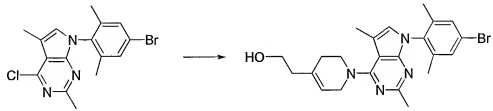
Synthesis of 2-{1-[1-(4-bromo-2,6-dimethylphenyl)-3,6-dimethyl-1H-pyrrolo[2,3-b]pyridin-4-yl]-1,2,3,6-tetrahydropyridin-4-yl}ethanol (compound 1-014)



A suspension of 1-(4-bromo-2,6-dimethylphenyl)-3,6-dimethyl-1H-pyrrolo[2,3-b]pyridin-4-ol (1.0 g), triethylamine (0.61 g) in $CHCl_3$ (20 mL), trifluoromethanesulfonic anhydride (0.61 mL) was added with cooling in an ice bath and the mixture was stirred for 30 minutes. A saturated aqueous $NaHCO_3$ solution was added to the reaction mixture and separated. The organic layer was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to obtain crude trifluoromethanesulfonic acid 1-(4-bromo-2,6-dimethylphenyl)-3,6-dimethyl-1H-pyrrolo[2,3-b]pyridin-4-yl ester (2.19 g). The crude trifluoromethanesulfonic acid 1-(4-bromo-2,6-dimethylphenyl)-3,6-dimethyl-1H-pyrrolo[2,3-b]pyridin-4-yl ester was dissolved in N-methylpyrrolidone (1.5 mL) and then 2-(1,2,3,6-tetrahydropyridin-4-yl)-ethanol (2.5 mL) and N,N-diisopropylethylamine (2.3 g) were added. The mixture was heated at 140 °C for 4 hours in a sealed tube. After cooling to room temperature, the reaction mixture was poured into a mixture of ethyl acetate and a saturated aqueous $NaHCO_3$ solution, and separated. The organic layer was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and the residue was purified with colomn chromatography (silica gel eluent: hexane : ethyl acetate = 1 / 1) to obtain a solid. The solid was washed with ethyl acetate to give the title compound (25 mg).

Example 2

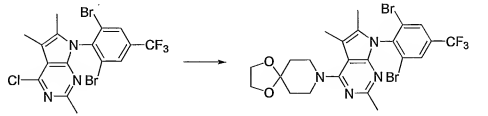
Synthesis of 2-{1-[7-(4-bromo-2,6-dimethylphenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-1,2,3,6-tetrahydropyridin-4-yl}ethanol (compound 1-013)



A mixture of 7-(4-bromo-2,6-dimethylphenyl)-4-chloro-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidine (1.0 g), 2-(1,2,3,6-tetrahydropyridin-4-yl)-ethanol (0.9 g) and N,N-diisopropylethylamine (1.1 g) was heated at 100°C for 5 hours in a sealed tube. After cooling to room temperature, the reaction mixture was poured into a mixture of ethyl acetate and a saturated aqueous $NaHCO_3$ solution, and separated. The organic layer was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and the residue was purified with colomn chromatography (silica gel eluent: hexane : ethyl acetate = 2 / 1) to obtain an solid. The solid was washed with ethyl acetate to give the title compound (69 mg).

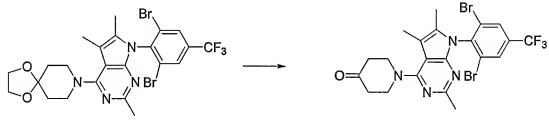
Example 3

Synthesis of {1-[7-(2,6-dibromo-4-trifluoromethyl-phenyl)-2,5,6-trimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-1,2,3,6-tetrahydro-pyridin-4-yl}-acetic acid (compound 1-015)

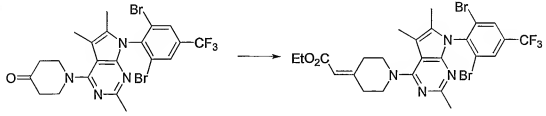


(1) A mixture of 4-chloro-7-(2,6-dibromo-4-trifluoromethyl-phenyl)-2,5,6-trimethyl-7H-pyrrolo[2,3-d]pyrimidine (5.0 g) and 4-piperidone ethylene ketal (3.0 g) in ethylene glycol (25 ml) was heated at 150°C for 30 minutes. After cooling to room temperature, the reaction mixture was poured into a mixture of ethyl acetate

and a saturated aqueous $NaHCO_3$ solution, and separated. The organic layer was washed with water three times and brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to give a solid and the solid was washed with isopropyl ether to give 8-[7-(2,6-dibromo-4-trifluoromethyl-phenyl)-2,5,6-trimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-1,4-dioxa-8-aza-spiro[4.5]decane (3.87 g).

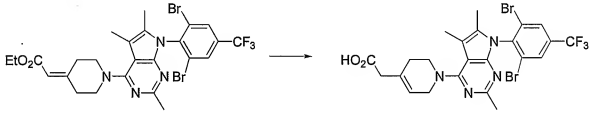


(2) A mixture of 8-[7-(2,6-dibromo-4-trifluoromethyl-phenyl)-2,5,6-trimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-1,4-dioxa-8-aza-spiro[4.5]decane (3.77 g) and 2.9 M HCl (10 ml) in THF (10 ml) was stirred at room temperature for 17 hours. To the mixture was added 2.9 M HCl (10 ml) and heated at 40 °C for 5 hours. The solvent was distilled off under reduced pressure, and the residue was made basic with a saturated aqueous $NaHCO_3$ solution, and extracted with ethyl acetate three times. The organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and the residue was purified with column chromatography (silica gel: Wako gel C200, eluent: hexane : ethyl acetate = 9 / 1) to obtain 1-[7-(2,6-dibromo-4-trifluoromethyl-phenyl)-2,5,6-trimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-piperidin-4-one (3.7 g) as amorphous.



(3) To a suspension of 60 % NaH (273 mg) in THF (10 ml) was added ethyl diethyl phosphonoacatate (1.7 g) under ice-cooling over a period of 3 minutes. The ice bath was removed, and the mixture was stirred at room temperature for 15 minutes. To the mixture was added a solution of 1-[7-(2,6-dibromo-4-trifluoromethyl-phenyl)-2,5,6-trimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-piperidin-4-one (3.49 g) in THF (10 ml) at room temperature over a period of 5

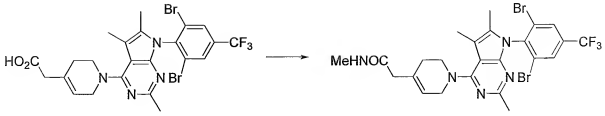
minutes and the mixture was stirred for 30 min. To the mixture was added a saturated aqueous NH_4Cl solution, and the THF was distilled off under reduced pressure. The residue was partitioned between ethyl acetate and brine, and the organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and the residue was purified with column chromatography (silica gel: Wako gel C200, eluent: hexane : ethyl acetate = 5 / 1) to obtain {1-[7-(2,6-dibromo-4-trifluoromethyl-phenyl)-2,5,6-trimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-piperidin-4-ylidene}-acetic acid ethyl ester (3.83 g) as amorphous.



(4) A mixture of {1-[7-(2,6-dibromo-4-trifluoromethyl-phenyl)-2,5,6-trimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-piperidin-4-ylidene}-acetic acid ethyl ester (2.22 g) and KOH (929 mg) in a mixture of water (1 ml) and EtOH (8 ml) was heated at 80°C for 1 hour. The reaction mixture was neutralized with 10 % HCl under ice-cooling and the solid precipitated was collected by filtration to obtain a mixture of {1-[7-(2,6-dibromo-4-trifluoromethyl-phenyl)-2,5,6-trimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-piperidin-4-ylidene}-acetic acid and {1-[7-(2,6-dibromo-4-trifluoromethyl-phenyl)-2,5,6-trimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-1,2,3,6-tetrahydro-pyridin-4-yl}-acetic acid. The mixture was separated and purified with column chromatography (silica gel: Wako gel C200, eluent: $CHCl_3$: MeOH = 40 / 1) to obtain the title compound (0.40 g) as a solid.

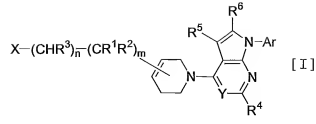
Example 4

Synthesis of 2-{1-[7-(2,6-dibromo-4-trifluoromethyl-phenyl)-2,5,6-trimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-1,2,3,6-tetrahydro-pyridin-4-yl}-N-methyl-acetamide (compound 1-017)



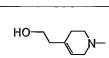
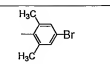
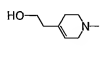
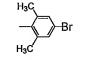
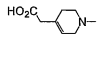
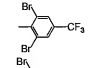
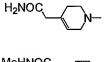
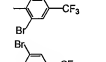
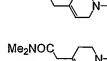
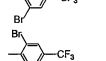
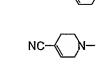
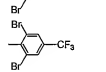
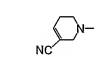
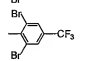
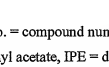
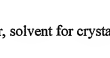
To a solution of {1-[7-(2,6-dibromo-4-trifluoromethyl-phenyl)-2,5,6-trimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-1,2,3,6-tetrahydro-pyridin-4-yl}-acetic acid (175 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (67 mg) and 1-hydroxybenzotriazole (67 mg) in DMF (1 ml) was added 40 % methylamine in water (30 ul) at room temperature and the mixture was stirred at room temperature for 12 hours. The reaction mixture was diluted with ethyl acetate, and washed with a saturated aqueous NH_4Cl solution, water and a saturated aqueous $NaHCO_3$ solution, dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and the residue was purified with column chromatography (silica gel: Wako gel C200, eluent: $CHCl_3$: MeOH = 30 / 1) to obtain a solid. The solid was washed with isopropyl ether to give the title compound (89 mg).

Table 1[*1]



[I]

Com. No.	Ex. No	X-(CHR^3)$_n$-(CR^{1}R^2)$_m$	Y	R^4	R^5	R^6	-Ar	melting point (°C) (solvent for crystallization)
1-001	2		N	CH_3	CH_3	CH_3		218-219[*2]
1-002	2		N	CH_3	CH_3	H		179-181 (EtOAc) [*3]
1-003	2		N	CH_3	CH_3	CH_3		135-137 (IPE/hexane)
1-004	2		N	CH_3	CH_3	H		177-179 (IPE)
1-005	2		N	CH_3	CH_3	CH_3		170-172 (IPE)
1-006	2		N	CH_3	CH_3	H		209-211 (IPE)
1-007	2		N	CH_3	CH_3	CH_3		amorphous
1-008	2		N	CH_3	CH_3	H		amorphous
1-009	2		N	CH_3	CH_3	CH_3		137-139 (IPE)
1-010	2		N	CH_3	CH_3	H		155-156 (IPE)
1-011	2		N	CH_3	CH_3	H		209-210
1-012	1		CH	CH_3	CH_3	H		159-161 (IPE/EtOAc)

1-013	2		N	CH_3	CH_3	H		172-174 (EtOAc)
1-014	1		CH	CH_3	CH_3	H		181-183 (EtOAc)
1-015	3		N	CH_3	CH_3	CH_3		amorphous
1-016	3		N	CH_3	CH_3	CH_3		156-157 (IPE)
1-017	3		N	CH_3	CH_3	CH_3		180-183 (IPE)
1-018	3		N	CH_3	CH_3	CH_3		amorphous
1-019	2		N	CH_3	CH_3	CH_3		amorphous
1-020	2		N	CH_3	CH_3	CH_3		amorphous

*1: Com. No. = compound number, Ex. No. = example number, solvent for crystallization: EtOAc = ethyl acetate, IPE = diisopropylether

Analytical data of non-crystal compounds are described below.

1-007:

MS (ES, Pos): 500 $(M + Na)^+$, 506 $(M + Na + 2)^+$; NMR (300 MHz, $CDCl_3$) δ 1.01 (6 H, t, J = 7.6 Hz), 1.93 (3 H, s), 1.95-2.20 (4 H, m), 2.37 (3 H, s), 2.48 (3 H, s), 2.51-2.64 (2 H, m), 3.61-3.72 (2 H, m), 4.12-4.24 (2 H, m), 6.77-6.88 (2 H, m).

1-008:

MS (ES, Pos): 486 $(M + Na)^+$, 488 $(M + Na + 2)^+$; NMR (300 MHz, $CDCl_3$) δ 1.02 (6 H, t, J = 7.6 Hz), 2.05-2.30 (4 H, m), 2.44 (3 H, d, J = 1.1 Hz), 2.49 (3 H, s), 2.51-2.67 (2 H, m), 3.67-3.78 (2 H, m), 4.18-4.30 (2 H, m), 6.60-6.63 (1 H, m), 6.82-6.89 (1 H, m), 7.35 (2 H, s).

1-015:

NMR (200 MHz, $CDCl_3$) δ 2.04 (3 H, s), 2.39 (3 H, s), 2.19-2.62 (2 H, m), 2.50 (3 H, s), 3.08-3.16 (2 H, m), 3.63-3.3.82 (2 H, m), 4.02-4.18 (2 H, m), 5.70-5.81 (1 H, m), 7.95 (1 H, d, J = 0.8 Hz).

1-018:

NMR (200 MHz, $CDCl_3$) δ 2.04 (3 H, s), 2.38 (3 H, s), 2.30-2.60 (2 H, m), 2.48 (3 H, s), 2.98 (3 H, s), 3.04 (3 H, s), 3.11-3.20 (2 H, m), 3.61-3.3.80 (2 H, m), 4.02-4.15 (2 H, m), 5.56-5.68 (1 H, m), 7.95 (2 H, s).

1-019:

MS (ES, Pos): 568 $(M + 1)^+$, 570 $(M + 3)^+$, 572 $(M + 5)^+$; NMR (300 MHz, $CDCl_3$) δ 2.06 (3 H, s), 2.36-2.42 (3 H, m), 2.49 (3 H, s), 2.58-2.68 (2 H, m), 3.68 (2 H, t, J = 5.5 Hz), 4.16-4.25 (2 H, m), 6.71-6.79 (1 H, m), 7.93-7.99 (2 H, m).

1-020:

MS (ES, Pos): 568 $(M + 1)^+$, 570 $(M + 3)^+$, 572 $(M + 5)^+$; NMR (300 MHz, $CDCl_3$) δ 2.06 (3 H, s), 2.36-2.42 (3 H, m), 2.50 (3 H, s), 2.53-2.62 (2 H, m), 3.68 (2 H, t, J = 5.7 Hz), 4.15-4.24 (2 H, m), 6.78-6.87 (1 H, m), 7.93-7.99 (2 H, m).

*2: The crystal was obtained after standing the compound purified with column chromatography.

*3: 1 HCl salt

Test Example [CRF receptor binding test]

Monkey amygdala membranes were used as a receptor preparation. ^{125}I-CRF was used as ^{125}I-labeled ligand.

Binding reaction using the ^{125}I-labeled ligand was carried out by the following method described in The Journal of Neuroscience, 7, 88 (1987).

Preparation of receptor membranes:

Monkey amygdala was homogenized in 50 mM Tris-HCl buffer (pH 7.0) containing 10 mM $MgCl_2$, 2 mM EDTA and centrifuged at 48,000 x g for 20 min, and the precipitate was washed once with Tris-HCl buffer. The washed precipitate was suspended in 50 mM Tris-HCl buffer (pH 7.0) containing 10 mM $MgCl_2$, 2 mM EDTA, 0.1% bovine serum albumin and 100 kallikrein units/ml aprotinin, to obtain a membrane preparation.

CRF receptor binding test:

The membrane preparation (0.3 mg protein/ml), ^{125}I-CRF (0.2 nM) and a test drug were reacted at 25°C for 2 hours. After completion of the reaction, the reaction mixture was filtered by suction through a glass filter (GF/C) treated with 0.3% polyethylene imine, and the glass filter was washed three times with phosphate-buffered saline containing 0.01% Triton X-100. After the washing, the radioactivity of the filter paper was measured in a gamma counter.

The amount of ^{125}I-CRF bound when the reaction was carried out in the presence of 1 μM CRF was taken as the degree of nonspecific binding of ^{125}I-CRF, and the difference between the total degree of ^{125}I-CRF binding and the degree of nonspecific ^{125}I-CRF binding was taken as the degree of specific ^{125}I-CRF binding. An inhibition curve was obtained by reacting a definite concentration (0.2 nM) of ^{125}I-CRF with various concentrations of each test drug under the conditions described above. A concentration of the test drug at which binding of ^{125}I-CRF is inhibited by 50% (IC_{50}) was determined from the inhibition curve.

As a result, it was found that compounds 1-001, 1-002, 1-005, 1-006, 1-007, 1-008, 1-009, 1-010, 1-012, 1-014 can be exemplified as typical compounds having an IC_{50} value of 100 nM or less.

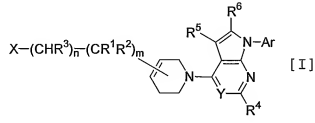
[EFFECT OF THE INVENTION]

According to the present invention, compounds having a high affinity for

CRF receptors have been provided. These compounds are effective against diseases in which CRF is considered to be involved, such as depression, anxiety, Alzheimer's disease, Parkinson's disease, Huntington's chorea, eating disorder, hypertension, gastrointestinal diseases, drug dependence, cerebral infarction, cerebral ischemia, cerebral edema, cephalic external wound, inflammation, immunity-related diseases, alopecia, irritable bowel syndrome, sleep disorders, epilepsy, dermatitides, schizophrenia, pain, etc.

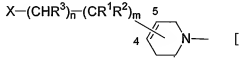
CLAIMS

1. A pyrrolopyrimidine or pyrrolopyridine derivative substituted with tetrahydropyridine represented by the following formula [I]:



[I]

(wherein the tetrahydropyridine is represented by the following formula [II]:



[II]

in which the tetrahydropyridine ring is substituted with a group represented by $-(CR^1R^2)_m-(CHR^3)_n-X$ at the 4-position or 5-position of the tetrahydropyridine ring;

X is hydroxy, cyano, $-CO_2R^7$ or $-CONR^{7a}R^{7b}$;

Y is N or CR^8;

with the proviso that when Y is CR^8, then X is hydroxy;

R^1 is hydrogen, hydroxy, C_{1-5}alkyl, C_{1-5}alkoxy-C_{1-5}alkyl or hydroxy-C_{1-5}alkyl;

R^2 is hydrogen or C_{1-5}alkyl;

R^3 is hydrogen, cyano, C_{1-5}alkyl, C_{1-5}alkoxy-C_{1-5}alkyl or hydroxy-C_{1-5}alkyl;

m is an integer selected from 0, 1, 2, 3, 4 and 5;

n is 0 or 1;

with the proviso that when X is hydroxy or $-CONR^{7a}R^{7b}$, and n is 0, then m is an integer selected from 1, 2, 3, 4 and 5;

R^4 is hydrogen, halogen, C_{1-5}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkyl-C_{1-5}alkyl, hydroxy, C_{1-5}alkoxy, C_{3-8}cycloalkyloxy or $-N(R^9)R^{10}$;

R^5 and R^6 are the same or different, and independently are hydrogen, halogen, C_{1-5}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkyl-C_{1-5}alkyl, hydroxy, C_{1-5}alkoxy,

C_{3-8}cycloalkyloxy, $-N(R^{11})R^{12}$, $-CO_2R^{13}$, cyano, nitro, C_{1-5}alkylthio, trifluoromethyl or trifluoromethoxy; or R^5 and R^6 are taken together to form $-CH_2-CH_2-CH_2-CH_2-$ or $-CH=CH-CH=CH-$;

with the proviso that when R^5 and R^6 are taken together to form $-CH_2-CH_2-CH_2-CH_2-$, then X is hydroxy;

R^7 is hydrogen or C_{1-5}alkyl;

R^{7a} and R^{7b} are the same or different, and independently hydrogen or C_{1-5}alkyl;

R^8 is hydrogen, C_{1-5}alkyl, halogen, cyano or $-CO_2R^{14}$;

R^9 and R^{10} are the same or different, and independently are hydrogen, C_{1-5}alkyl, C_{3-8}cycloalkyl or C_{3-8}cycloalkyl-C_{1-5}alkyl;

R^{11} and R^{12} are the same or different, and independently are hydrogen, C_{1-5}alkyl, C_{3-8}cycloalkyl or C_{3-8}cycloalkyl-C_{1-5}alkyl;

R^{13} is hydrogen or C_{1-5}alkyl;

R^{14} is hydrogen or C_{1-5}alkyl;

Ar is aryl or heteroaryl which aryl or heteroaryl is unsubstituted or substituted with 1 or more substituents, which are the same or different, selected from the group consisting of halogen, C_{1-5}alkyl, C_{3-8}cycloalkyl, C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-5}alkoxy, C_{1-5}alkylthio, C_{1-5}alkylsulfinyl, C_{1-5}alkylsulfonyl, cyano, nitro, hydroxy, $-CO_2R^{15}$, $-C(=O)R^{16}$, $-CONR^{17}R^{18}$, $-OC(=O)R^{19}$, $-NR^{20}CO_2R^{21}$, $-S(O)_2NR^{22}R^{23}$, trifluoromethyl, trifluoromethoxy, difluoromethoxy, fluoromethoxy, methylenedioxy, ethylenedioxy and $-N(R^{24})R^{25}$;

R^{15} is hydrogen, C_{1-5}alkyl, C_{3-8}cycloalkyl or C_{3-8}cycloalkyl-C_{1-5}alkyl;

R^{16} is hydrogen or C_{1-5}alkyl;

R^{17} and R^{18} are the same or different, and independently are hydrogen, C_{1-5}alkyl, C_{3-8}cycloalkyl or C_{3-8}cycloalkyl-C_{1-5}alkyl;

R^{19} is hydrogen or C_{1-5}alkyl;

R^{20} is hydrogen or C_{1-5}alkyl;

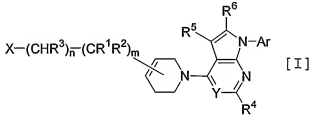
R^{21} is hydrogen or C_{1-5}alkyl;

R^{22} and R^{23} are the same or different, and independently are hydrogen, C_{1-5}alkyl, C_{3-8}cycloalkyl or C_{3-8}cycloalkyl-C_{1-5}alkyl;

R^{24} and R^{25} are the same or different, and independently are hydrogen, C_{1-5}alkyl, C_{3-8}cycloalkyl or C_{3-8}cycloalkyl-C_{1-5}alkyl;

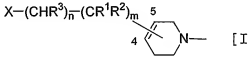
r is 1 or 2), individual isomers thereof, racemic or non-racemic mixtures of isomers thereof or N-oxide thereof, or pharmaceutically acceptable salts and hydrates thereof.

2. A pyrrolopyrimidine or pyrrolopyridine derivative substituted with tetrahydropyridine represented by the following formula [I]:



[I]

(wherein the tetrahydropyridine is represented by the following formula [II]:



[II]

in which the tetrahydropyridine ring is substituted with a group represented by $-(CR^1R^2)_m-(CHR^3)_n-X$ at the 4-position or 5-position of the tetrahydropyridine ring;

X is hydroxy, cyano or $-CO_2R^7$;

Y is N or CR^8;

with the proviso that when Y is CR^8, then X is hydroxy;

R^1 is hydrogen, hydroxy, C_{1-5}alkyl, C_{1-5}alkoxy-C_{1-5}alkyl or hydroxy-C_{1-5}alkyl;

R^2 is hydrogen or C_{1-5}alkyl;

R^3 is hydrogen, cyano, C_{1-5}alkyl, C_{1-5}alkoxy-C_{1-5}alkyl or hydroxy-C_{1-5}alkyl;

m is an integer selected from 0, 1, 2, 3, 4 and 5;

n is 0 or 1;

with the proviso that when X is hydroxy, and n is 0, then m is an integer selected from 1, 2, 3, 4 and 5;

R^4 is hydrogen, C_{1-5}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkyl-C_{1-5}alkyl, hydroxy, C_{1-5}alkoxy, C_{3-8}cycloalkyloxy or $-N(R^9)R^{10}$;

R^5 and R^6 are the same or different, and independently are hydrogen, halogen, C_{1-5}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkyl-C_{1-5}alkyl, hydroxy, C_{1-5}alkoxy, C_{3-8}cycloalkyloxy, $-N(R^{11})R^{12}$, $-CO_2R^{13}$, cyano, nitro, C_{1-5}alkylthio, trifluoromethyl or trifluoromethoxy; or R^5 and R^6 are taken together to form $-CH_2-CH_2-CH_2-CH_2-$ or $-CH=CH-CH=CH-$;

with the proviso that when R^5 and R^6 are taken together to form $-CH_2-CH_2-CH_2-CH_2-$, then X is hydroxy;

R^7 is hydrogen or C_{1-5}alkyl;

R^8 is hydrogen, C_{1-5}alkyl, halogen, cyano or $-CO_2R^{14}$;

R^9 and R^{10} are the same or different, and independently are hydrogen, C_{1-5}alkyl, C_{3-8}cycloalkyl or C_{3-8}cycloalkyl-C_{1-5}alkyl;

R^{11} and R^{12} are the same or different, and independently are hydrogen, C_{1-5}alkyl, C_{3-8}cycloalkyl or C_{3-8}cycloalkyl-C_{1-5}alkyl;

R^{13} is hydrogen or C_{1-5}alkyl;

R^{14} is hydrogen or C_{1-5}alkyl;

Ar is aryl or heteroaryl which aryl or heteroaryl is unsubstituted or substituted with 1 or more substituents, which are the same or different, selected from the group consisting of halogen, C_{1-5}alkyl, C_{3-8}cycloalkyl, C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-5}alkoxy, C_{1-5}alkylthio, C_{1-5}alkylsulfinyl, C_{1-5}alkylsulfonyl, cyano, nitro, hydroxy, $-CO_2R^{15}$, $-C(=O)R^{16}$, $-CONR^{17}R^{18}$, $-OC(=O)R^{19}$, $-NR^{20}CO_2R^{21}$, $-S(O)_2NR^{22}R^{23}$, trifluoromethyl, trifluoromethoxy, difluoromethoxy, fluoromethoxy, methylenedioxy, ethylenedioxy and $-N(R^{24})R^{25}$;

R^{15} is hydrogen, C_{1-5}alkyl, C_{3-8}cycloalkyl or C_{3-8}cycloalkyl-C_{1-5}alkyl;

R^{16} is hydrogen or C_{1-5}alkyl;

R^{17} and R^{18} are the same or different, and independently are hydrogen, C_{1-5}alkyl, C_{3-8}cycloalkyl or C_{3-8}cycloalkyl-C_{1-5}alkyl;

R^{19} is hydrogen or C_{1-5}alkyl;

R^{20} is hydrogen or C_{1-5}alkyl;

R^{21} is hydrogen or C_{1-5}alkyl;

R^{22} and R^{23} are the same or different, and independently are hydrogen, C_{1-5}alkyl, C_{3-8}cycloalkyl or C_{3-8}cycloalkyl-C_{1-5}alkyl;

R^{24} and R^{25} are the same or different, and independently are hydrogen, C_{1-5}alkyl, C_{3-8}cycloalkyl or C_{3-8}cycloalkyl-C_{1-5}alkyl;

r is 1 or 2), individual isomers thereof, racemic or non-racemic mixtures of isomers thereof or N-oxide thereof, or pharmaceutically acceptable salts and hydrates thereof.

3. The pyrrolopyrimidine derivative substituted with the tetrahydropyridine according to claim 2 represented by formula [I], wherein Y is N; X, m, n, R^1, R^2, R^3, R^4, R^5, R^6 and Ar are as defined in claim 2; individual isomers thereof or racemic or non-racemic mixtures of isomers thereof, or pharmaceutically acceptable salts and hydrates thereof.

4. The pyrrolopyrimidine derivative substituted with the tetrahydropyridine according to claim 2 represented by formula [I], wherein Y is N; X is hydroxy; m is an integer selected from 1, 2, 3, 4 and 5; n is 0; R^1 and R^2 are hydrogen; R^4, R^5, R^6 and Ar are as defined in claim 2; individual isomers thereof or racemic or non-racemic mixtures of isomers thereof, or pharmaceutically acceptable salts and hydrates thereof.

5. The pyrrolopyrimidine derivative substituted with the tetrahydropyridine according to claim 2 represented by formula [I], wherein Y is N; X is hydroxy; m is an integer selected from 1, 2 and 3; n is 0; R^1 and R^2 are hydrogen; R^4 is $C_{1\text{-}5}$alkyl; R^5 and R^6 are the same or different, and independently are hydrogen or $C_{1\text{-}5}$alkyl; Ar is phenyl which phenyl is substituted with two or three substituents, which are the same or different, selected from the group consisting of halogen, $C_{1\text{-}3}$alkyl, $C_{1\text{-}3}$alkoxy, $C_{1\text{-}3}$alkylthio, trifluoromethyl, trifluoromethoxy and $-N(R^{24})R^{25}$ (wherein R^{24} and R^{25} are the same or different, and independently are hydrogen or $C_{1\text{-}3}$alkyl); individual isomers thereof or racemic or non-racemic mixtures of isomers thereof, or pharmaceutically acceptable salts and hydrates thereof.

6. The pyrrolopyrimidine derivative substituted with the tetrahydropyridine according to claim 2 represented by formula [I], wherein Y is N; X is cyano; R^1, R^2 and R^3 are hydrogen; m, n, R^4, R^5, R^6 and Ar are as defined in claim 2; individual isomers thereof or racemic or non-racemic mixtures of isomers thereof, or pharmaceutically acceptable salts and hydrates thereof.

7. The pyrrolopyrimidine derivative substituted with the tetrahydropyridine according to claim 2 represented by formula [I], wherein Y is N; X is cyano; m is 0 or 1; n is 0; R^1 and R^2 are hydrogen; R^4 is C_{1-5}alkyl; R^5 and R^6 are the same or different, and independently are hydrogen or C_{1-5}alkyl; Ar is phenyl which phenyl is substituted with two or three substituents, which are the same or different, selected from the group consisting of halogen, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkylthio, trifluoromethyl, trifluoromethoxy and $-N(R^{24})R^{25}$ (wherein R^{24} and R^{25} are the same or different, and independently are hydrogen or C_{1-3}alkyl); individual isomers thereof or racemic or non-racemic mixtures of isomers thereof, or pharmaceutically acceptable salts and hydrates thereof.

8. The pyrrolopyridine derivative substituted with the tetrahydropyridine according to claim 2 represented by formula [I], wherein Y is CR^8; X is hydroxy; m, n, R^1, R^2, R^3, R^4, R^5, R^6, R^8 and Ar are as defined in claim 2; individual isomers thereof or racemic or non-racemic mixtures of isomers thereof, or pharmaceutically acceptable salts and hydrates thereof.

9. The pyrrolopyridine derivative substituted with the tetrahydropyridine according to claim 2 represented by formula [I], wherein Y is CH; X is hydroxy; m is an integer selected from 1, 2, 3, 4 and 5; n is 0; R^1 and R^2 are hydrogen; R^4, R^5, R^6 and Ar are as defined in claim 2; individual isomers thereof or racemic or non-racemic mixtures of isomers thereof, or pharmaceutically acceptable salts and hydrates thereof.

10. The pyrrolopyridine derivative substituted with the tetrahydropyridine according to claim 2 represented by formula [I], wherein Y is CH; X is hydroxy; m is an integer selected from 1, 2 and 3; n is 0; R^1 and R^2 are hydrogen; R^4 is C_{1-5}alkyl; R^5 and R^6 are the same or different, and independently are hydrogen or C_{1-5}alkyl; Ar is phenyl which phenyl is substituted with two or three substituents, which are the same or different, selected from the group consisting of halogen, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkylthio, trifluoromethyl, trifluoromethoxy and $-N(R^{24})R^{25}$ (wherein R^{24} and R^{25} are the same or different, and independently are hydrogen or

C_{1-3}alkyl); individual isomers thereof or racemic or non-racemic mixtures of isomers thereof, or pharmaceutically acceptable salts and hydrates thereof.

11. An antagonist for CRF receptors, comprising a pyrrolopyrimidine or pyrrolopyridine derivative substituted with tetrahydropyridine, a pharmaceutically acceptable salt thereof or its hydrate according to any one of claims 1 to 10, as an active ingredient.

12. Use of a pyrrolopyrimidine or pyrrolopyridine derivative substituted with tetrahydropyridine, a pharmaceutically acceptable salt thereof or its hydrate according to any one of claim 1 to 10, for the manufacture of an antagonist for CRF receptors.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP2005/012141

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/04 C07D487/04 A61K31/437 A61K31/519 A61P25/00
//(C07D471/04,221:00,209:00),(C07D487/04,239:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02/02549 A (TAISHO PHARMACEUTICAL CO., LTD; NAKAZATO, ATSURO; KUMAGAI, TOSHIHITO;) 10 January 2002 (2002-01-10) cited in the application claims 1,2,8-13; tables 12,20 reaction schemes 2-4,7 examples 4(4),5(4)	1-12
Y	EP 1 176 146 A (TAISHO PHARMACEUTICAL CO., LTD) 30 January 2002 (2002-01-30) cited in the application paragraph '0001!; claim 1; table 1	1-12
Y	WO 02/088095 A (GLAXO GROUP LIMITED; CAPELLI, ANNA, MARIA; DI FABIO, ROMANO; MARCHIONN) 7 November 2002 (2002-11-07) claims 1,23	1-5,8-12

-/—

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 October 2005	28. 10. 05

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seymour, L

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP2005/012141

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	HSIN L-W ET AL: "CRHR1 Receptor binding and lipophilicity of pyrrolopyrimidines, potential nonpeptide corticotropin-releasing hormone type 1 receptor antagonists" BIOORGANIC & MEDICINAL CHEMISTRY, ELSEVIER SCIENCE LTD, GB, vol. 10, 2002, pages 175-183, XP002275670 ISSN: 0968-0896 compounds 17 and 18; table 1	1-5,8-12
P,Y	WO 2004/058767 A (TAISHO PHARMACEUTICAL CO., LTD; NAKAZATO, ATSURO; OKUBO, TAKETOSHI; NO) 15 July 2004 (2004-07-15) cited in the application claims 1,41,43	1-12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2005/012141

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-3(part),4,5,8-10,11(part),12(part)

   Compounds of formula I where X is OH and corresponding compositions and uses

   ---

2. claims: 1-3(part),6,7,11(part),12(part)

   Compounds of formula I where X is cyano or -CO2R7 and corresponding compositions and uses

   ---

3. claims: 1(part),11(part),12(part)

   Compounds of formula I where X is -CONR7aR7b and corresponding compositions and uses

   ---

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/JP2005/012141

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0202549 A	10-01-2002	AU 6943701 A	14-01-2002
		BG 107374 A	30-09-2004
		BR 0112166 A	02-09-2003
		CA 2412287 A1	10-01-2002
		CN 1439001 A	27-08-2003
		CN 1535968 A	13-10-2004
		CZ 20024229 A3	18-06-2003
		EA 5289 B1	30-12-2004
		EE 200300007 A	16-08-2004
		EP 1299378 A1	09-04-2003
		HR 20030074 A2	28-02-2005
		HU 0301165 A2	28-08-2003
		JP 2004502685 T	29-01-2004
		MX PA02012820 A	14-05-2003
		NO 20026125 A	04-02-2003
		PL 358411 A1	09-08-2004
		SK 132003 A3	05-08-2003
		TW 591022 B	11-06-2004
		US 2004034061 A1	19-02-2004
EP 1176146 A	30-01-2002	AT 297393 T	15-06-2005
		AU 756702 B2	23-01-2003
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